Table S1. Comparative Landscape of Generative Models for Immune Receptor and Construct Design

Model / Framework	Primary Input Data	Core Architecture	Output Type	Open-Source Status	Typical Use Case	Relevance to TCR-T	Relevance to CAR-T
ESM-2	Protein sequences (millions), optional MSAs	Transformer-based protein language model	Sequence embeddings; generated sequences	Open-source (GitHub: Meta AI ESM)	Sequence generation, mutational scanning, representation learning	High: TCR sequence modeling, CDR diversity exploration	Low–Moderate
MSA Transformer	Multiple sequence alignments	Transformer with evolutionary attention	Sequence representations conditioned on MSAs	Open-source (GitHub: FacebookResearch MSA-Transformer)	Evolutionary constraint modeling	Moderate	Low
ProteinMPNN	Protein backbone structures	GNN / autoregressive model	Structure-compatible sequences	Open-source (GitHub: ProteinMPNN)	Sequence design from fixed folds	High	Moderate
RFdiffusion	Protein structures or motifs	Diffusion model with geometry constraints	3D protein structures	Open-source (GitHub: Rosetta RFdiffusion)	De novo binder design	Moderate	High
Chroma	Structure + sequence	Diffusion-based model	3D protein structures and sequences	Open-source (GitHub: GenerateBio Chroma)	Flexible constrained design	Low–Moderate	Moderate
PhysicoGPTCR	TCR seq + antigen + physicochemical features	Transformer with conditioning	Antigen-aware TCR sequences	Research prototype; partial or study-specific release	Targeted TCR design	Very High	Not designed
ProteinMPNN-TCR	TCR–pMHC structures	Fine-tuned ProteinMPNN	Interface-aware TCR sequences	Research prototype; study-specific adaptation of ProteinMPNN	Structural TCR redesign	Very High	Low
Generative CAR frameworks	CAR libraries + functional data	Transformer / RL hybrids	Modular CAR designs	Mostly proprietary / study-specific; code not publicly released	CAR optimization	Low	Very High

Table S2. From Conventional Immunotherapy to Generative Immunoengineering

Dimension	Conventional Immunotherapy Paradigm	Generative Immunoengineering Paradigm
Design Logic	Empirical discovery based on trial-and-error antigen selection and screening.	Computational generation guided by probabilistic models of receptor–antigen interaction and cellular behavior.
Underlying Assumption	Assumes optimal therapeutic solutions already exist within naturally evolved immune repertoires and can be identified through screening, selection, and incremental optimization.	Assumes the functional immune solution space is continuous, learnable, and extrapolatable beyond naturally observed examples, enabling algorithmic generation of novel receptors, circuits, and cellular states.
Data Utilization	Limited to experimental assays and patient-level outcomes.	Integrates multi-omic, structural, and clinical data into unified embeddings for design and prediction.
Optimization Process	Manual iterative testing; low throughput; human-driven decision cycles.	Automated optimization via active learning, reinforcement signals, and adaptive design–build–test–learn (DBTL) loops.
Scope of Design	Focused on single-target molecules or cell products.	System-level generation of receptors, circuits, and cellular phenotypes across multiple design objectives.
Experimental Feedback	Linear workflow: hypothesis → test → validation.	Closed feedback loop: generative output → experimental validation → model retraining → improved design.
Time Scale	Months to years from concept to candidate validation.	Days to weeks with parallel computational synthesis and in-silico pre-screening.
Interpretability	Dependent on mechanistic intuition; limited transparency in design rationale.	Explainable AI and mechanistic priors enable causal insight alongside prediction.
Manufacturing Integration	Separated from design; manual scale-up.	Digitally linked to automated biofoundries with algorithmic quality control and digital-twin monitoring.

Regulatory Context	Static approval for fixed molecular entities.	Continuous validation and lifecycle oversight for adaptive, learning-based therapeutics.
Ethical Dimension	Reactive regulation; limited data transparency.	Embedded ethical governance: consent tracking, data provenance, and algorithmic accountability.

Table S3. Translational Matrix: Applications and Targets of Generative Immunoengineering.

Therapeutic Domain	Generative Design Strategy	Example Construct / Approach	Translational Stage	Clinical or Strategic Goal	References
Oncology	AI-driven receptor optimization for high-affinity, tumor-specific binding.	Multispecific or logic-gated CAR-T cells integrating affinity tuning and cytokine-controlled feedback.	Preclinical → Early-phase clinical trials.	Increase tumor selectivity, persistence, and safety; mitigate off-tumor toxicity.	[117,251]
Autoimmune Disorders	Generative modeling of regulatory-cell circuits to restore immune tolerance.	Synthetic regulatory T (Treg) or tolerogenic dendritic-cell designs with cytokine-balanced circuits.	Preclinical / proof-of-concept.	Suppress autoimmunity without broad immunosuppression.	[252,253]
Regenerative Medicine	AI-guided macrophage or APC reprogramming for tissue repair and graft tolerance.	Engineered macrophages producing pro-resolving mediators and metabolic-stability signatures.	Early preclinical studies.	Enhance regeneration, reduce fibrosis, and improve graft acceptance.	[254]

Infectious Disease & Vaccinology	Rapid generative design of receptor and antigen pairs using diffusion or language models.	Model-driven epitope design for next-generation vaccine candidates.	Preclinical / candidate identification.	Accelerate immune-response optimization to emerging pathogens.	[251,255]
Transplant Immunology	Generative modeling for donor–recipient immune matching and synthetic tolerance induction.	Predictive receptor generation minimizing alloreactivity; tolerance-inducing T-cell circuits.	Conceptual / exploratory.	Prevent graft rejection and chronic inflammation.	[256,257]
Immuno-Oncology Combinations	System-level optimization of multi-agent intervention.	Co-designed CAR-T + checkpoint-modulator constructs governed by reinforcement learning.	Translational modeling / phase I design.	Harmonize multi-modal immunotherapy dynamics.	[258,259]